Multilevel somatosensory system disinhibition in children with migraine

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Abstract

Although migraine is characterised by an abnormal cortical excitability level, whether the central nervous system is hyper- or hypo-excititable in migraine still remains an unsolved problem. The aim of our study was to compare the somatosensory evoked potential (SEP) recovery cycle, a marker of the somatosensory system’s excitability, in a group of 15 children suffering from migraine without aura (MO) (mean age 11.7 ± 1.6 years, five males, 10 females) and 10 control age-matched subjects (CS) (mean age 10.9 ± 2.1 years, six males, four females). We calculated the SEP’s latency and amplitude modifications after paired electrical stimuli at 5, 20 and 40 ms interstimulus intervals (ISIs), comparing it with a single stimulus condition assumed as the baseline. In MO patients, the amplitudes of the cervical N13 and of the cortical N20, P24 and N30 responses at 20 and 40 ms ISIs showed a higher recovery than in CS (two-way ANOVA, P < 0.05). Since, the SEP recovery cycle depends on the inhibitory interneuron function, our findings suggest that a somatosensory system disinhibition takes place in migraine. This is a generalized phenomenon, not limited to the cerebral cortex, but concerning also the cervical grey matter. The SEP recovery cycle reflects the intracellular concentration of Na⁺, therefore, the shortened recovery cycle in our MO patients suggests a high level of intracellular Na⁺ and a consequent depolarized resting membrane potential, possibly due to an impaired Na⁺–K⁺ ATPase function in migraine.

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1. Introduction

In migraine, the reduced habituation to the afferent inputs during the interictal phase is one of the most characteristic neurophysiological features (see Ambrosini et al., 2003; Schoenen et al., 2003 for reviews). Due to habituation, the evoked potential (EP) amplitude, which is a quantitative index of the neuronal population activated by certain sensory inputs, tends to decrease during repetitive sensory stimulation, due to a progressive reduction of the neuronal response. In migraine, experimental studies aiming at the investigation of the EP modification after repetitive stimulation showed a lack of habituation in both children and adults (Afra et al., 1998, 2000; Evers et al., 1997, 1998; Grosser et al., 2000; Maertens de Noordhout et al., 1986; Ozkul and Uckardes, 2002; Sand and Vingen, 2000; Sartory et al., 1997; Valeriani et al., 2003). This phenomenon was believed to be caused either by an increased or by a reduced cortical excitability. The threshold for phosphene induction by transcranial magnetic stimulation of the occipital cortex, lower in patients with migraine than in healthy subjects, suggests that in the former group the brain is hyperexcitable (Aurora et al., 1998). However, Bohotin et al. (2002) recently demonstrated the recovery of a normal habituation pattern of the P100 visual evoked potential (VEP) in migraineurs after high frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) of the occipital cortex. On the contrary, control subjects submitted to low frequency (1 Hz) rTMS of the occipital cortex showed no P100 amplitude habituation. Since, the rTMS at 10 Hz and at 1 Hz, respectively, increases and reduces the cortical excitability, the authors suggested that migraineurs show a normal habituation when their cortical excitability is raised up to the level of healthy subjects, who, on the contrary, lose the VEP habituation if their occipital cortex is inhibited. According to these results, in the interictal phase of migraine there is a cortical hypoexcitability, and the lack
of habituation can be explained by the ‘ceiling effect model’
(Knott and Irwin, 1973; Schoenen, 1996). In this model, the
habituation depends on the pre-activation level of the
cerebral cortex, which is very low in migraine, and prevents
any further excitability reduction.

A marker of the SI area excitability is represented by the
SEP recovery cycle. It is known that when SEPs are
obtained by two paired electrical shocks at different
interstimulus intervals (ISIs), the SEP amplitude evoked
by the later stimulus is smaller than the one recorded from a
single stimulus. The longer is the ISI, the higher is the
amplitude of the SEPs recorded after the second stimulus,
until a complete amplitude recovery is observed (Angel
et al., 1985; Emori et al., 1991; Meyer-Hardting et al., 1983;
Romani et al., 1995; Shagass and Schwartz, 1964). The aim
of our study was to investigate the SEP recovery cycle in
patients with migraine. According to our hypothesis, if the
excitability of the SI area is increased in migraine, the
recovery of the SEP amplitude should take a shorter time in
migraineurs than in healthy subjects.

2. Materials and methods

2.1. Subjects

Twenty-five subjects, whose parents gave an informed consent,
took part in this study. Fifteen patients had migraine without aura
(MO) (mean age 11.7 ± 1.6 years, five males, 10 females) and 10
healthy children were the control subjects (CS) (mean age 10.9 ±
2.1 years, six males, four females). MO patients were diagnosed
according to the criteria of the International Headache Society
(2004). All of them had had the first migraine attack at least 1 year
before being included in our study. We made sure that they did not
suffer from any other neurological or internal disease. The SEP
recordings were performed no sooner than 72 h after the last
headache attack. Moreover, in no patient a headache attack
followed the SEP recording in the next 72 h. No MO patient took
any drug during the 72 h before the SEP recording was performed.
In selecting the CS, children whose first- or second-degree relatives
suffered from migraine were excluded from the study.

2.2. SEP recording

For SEP recording, subjects lay in a couch in a quiet and
semidarkened room. Right and left median nerves were stimulated
at the wrist by surface electrodes at an intensity just able to produce
a motor twitch (stimulus duration: 0.2 ms, stimulus rate: 2 Hz).
SEPs were recorded from four electrodes (impedance <5 kΩ)
placed: (1) at Erb’s point ipsilateral to the stimulation (Erb),
referred to an electrode at the contralateral Erb’s point (Erbc);
(2) over the 6th cervical vertebra (C6), referred to an anterior electrode
above the thyroid cartilage (AC); (3) over the parietal area
contralateral to the stimulation (P3/P4); (4) over the frontal midline
(Fz). The scalp electrodes were referred to an electrode at the
earlobe ipsilateral to the stimulated side (Au1/Au2). The ground
was at the stimulated arm. The analysis time was 100 ms, with a
sampling rate of 20 kHz. The amplifier band-pass was 10–2000 Hz
(12 dB roll-off). One average of 1000 trials was obtained in each
of the conditions (i.e. single stimulus or double stimulus) and
printed out.

2.3. SEP recovery cycle

For investigating the SEP recovery cycle, we used a paired
stimulation technique, similar to that of previous studies (Emori
et al., 1991; Meyer-Hardting et al., 1983). SEP recording to a
single stimulus was taken as control. Moreover, three further
recordings were performed by using two paired stimuli at different
ISIs (5, 20, and 40 ms). In the double-stimulus traces, the responses
following the second stimulation were obtained by subtracting the
control SEP waveforms from the waveforms following each
double stimulus.

2.4. SEP analysis

SEPs were identified according to their latency and polarity. The peripheral N9 potential was recorded by the Erb electrode,
while the spinal N13 response was identified in the C6-AC trace.
Both scalp electrodes (P3/P4 and Fz) recorded the lemniscal P14
component, which was measured in the frontal trace where it
shows the highest amplitude (Restuccia et al., 1995). The parietal
N20 and P24 responses were recognizable in the parietal trace,
while the N30 potential was recorded by the frontal lead. SEP
amplitude was measured from the previous peak of opposite
polarity. SEP latencies and amplitudes following a single stimulus,
recorded both on the left and right side of the subject, were
compared by using the paired Student’s t-test and the Wilcoxon
test, respectively. In the single stimulus condition, the unpaired
Student’s t-test and the Mann–Whitney test were performed to
compare SEP latencies and amplitudes respectively among MO
patients and CS. Two-way ANOVA was used to compare the
recovery cycle of the SEP latencies among MO patients and CS, by
considering the group (i.e. patients or CS) and the ISI as sources of
variability. In order to reveal possible differences between the SEP
amplitude recovery cycle of MO patients and that of the CS, the
SEP amplitudes in the double stimulus conditions were normalized
as the percentage of the corresponding SEP amplitude obtained
after a single stimulus, which was assumed as 100%. The SEP
amplitudes to double stimuli at different ISIs were then compared
by means of the two-way ANOVA, considering the subject group
(patients or CS) and the ISI as variables. Post hoc analysis was
performed by means of the Student’s t-test with Bonferroni’s
correction for multiple comparisons. Amplitudes of the cortical
SEP components (N20, P24 and N30) were compared to the
lemniscal P14 component at the ISIs of 20 and 40 ms by using the
Spearman’s correlation test, in order to make sure that the recovery
cycle of the cortical potentials did not depend on the one of the
brainstem P14 response. The level for statistical significance was
fixed at P < 0.05.

3. Results

3.1. SEP amplitude and latency

In the single stimulus condition, the comparison of SEP
amplitudes and latencies recorded from the two sides
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